IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

IN RE: GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS (GLP-1 RAs) PRODUCTS LIABILITY LITIGATION	:	**CIVIL ACTION**
THIS DOCUMENT RELATES TO:	:	**MDL No. 3094**
ALL ACTIONS / ALL CASES	:	**2:24-md-03094-KSM**

NOVO NORDISK'S MEMORANDUM OF LAW IN SUPPORT OF ITS MOTION TO EXCLUDE THE OPINIONS AND TESTIMONY OF DRS. DANIEL RAINES AND ELIOT SIEGEL

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

Rules

Other Authorities

INTRODUCTION

From the start, the focus of this litigation has been on chronic gastroparesis, a disease characterized by severe, persistent gastrointestinal symptoms and delayed gastric emptying, caused by injury to the stomach's nerves and/or muscles. Indeed, among more than 800 Plaintiff Fact Sheets alleging gastroparesis, approximately 96% say that the Plaintiff's condition continues unresolved. *See* Declaration of L. Przymusinski, M.D., J.D., ¶ 18. Accordingly, Defendants expected Plaintiffs' experts to attempt to make the case that a diagnosis of chronic gastroparesis can be made without an objective gastric emptying study.

Remarkably, none of Plaintiffs' experts offers that opinion. In fact, they concede it is the consensus of the medical community that a diagnosis of chronic gastroparesis—regardless of its cause—requires objective evidence of delayed gastric emptying, obtained by way of scintigraphy, breath test, or wireless capsule testing. Accordingly, it is undisputed that Plaintiffs alleging chronic gastroparesis as their injury—which appear to be the overwhelming majority—must come forward with objective evidence to support their claim.

Instead, Plaintiffs' experts pivot and opine that there is an exception to the diagnostic testing requirement in cases involving a transient condition they describe as "drug-induced gastroparesis." They contend this condition differs from chronic gastroparesis in that symptom onset occurs after use of the medicine, symptoms typically resolve within a matter of weeks after medication cessation, and a gastric emptying study is not needed to make a diagnosis.

Plaintiffs' experts' "methodologies" for diagnosing this temporary form of gastroparesis—as disclosed in their reports and at deposition—are unreliable and should be excluded under *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), and Federal Rule of Evidence 702. As a threshold matter, the "methodologies" lack key indicia of reliability under *Daubert*, never have been published, tested, or subjected to peer review, have no known error rate, and are

at odds with the diagnostic criteria for gastroparesis accepted by all major gastroenterology societies in the United States and internationally. *See Daubert*, 509 U.S. at 590. The "methodologies" also are entirely subjective—lacking any standards or requirements that could be tested or verified by others—and are predicated solely on a vague temporal relationship between symptoms and medication use. *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 745 (3d Cir. 1994).

Furthermore, these experts' "methodologies" are premised on an unsupported analytical leap from non-specific gastrointestinal symptoms to a diagnosis of drug-induced gastroparesis. In applying their "methodologies," both experts simply ***assume*** that gastrointestinal symptoms occurring in patients taking GLP-1RAs—such as nausea, vomiting, abdominal pain or bloating—are caused by the medications' effect on gastric emptying. But it is well established that gastrointestinal side effects may occur for many reasons independent of delayed gastric emptying. In fact, the only study Plaintiffs' experts cite involving GLP-1RAs which evaluated the relationship between gastrointestinal symptoms and gastric emptying found that nearly two-thirds of patients on GLP-1RAs who experienced gastrointestinal symptoms did not have delayed gastric emptying, indicating that their symptoms were a result of something other than a medication effect on gastric emptying. Lupianez-Merly 2024, Ex. A.[1] As this study indicates, Plaintiffs' experts' assumption that gastrointestinal symptoms in patients taking GLP-1RAs are indicative of delayed gastric emptying would be wrong 65% of the time. A method with an error rate of this magnitude cannot provide a reliable basis for diagnosing gastroparesis or any other condition. *See Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997).

[1] All exhibits set forth in this Memorandum are attached to the March 5, 2025 Declaration of Lucas P. Przymusinski, M.D., J.D.

For these reasons, and as discussed below and in Lilly's Brief, the Court should exclude Plaintiffs' experts' opinions related to diagnosis of "drug-induced gastroparesis" under Rule 702 and *Daubert.*

BACKGROUND

I. GASTROPARESIS AND ITS CAUSES.

Gastroparesis is a motility disorder characterized by symptoms and objective evidence of delayed gastric emptying of solid food without mechanical obstruction.[2] *See* Camilleri 2022, Ex. B; Camilleri 2013, Ex. C. Gastroparesis may develop as the result of any pathology that causes injury or dysfunction of the gastric smooth muscle, the nerves that serve the stomach, or both. *See* Raines Rpt., Ex. D, at 6. Known causes of gastroparesis include diabetes, surgery, hypothyroidism, dysautonomia, certain autoimmune and connective tissue disorders, certain nervous system disorders, and certain viral infections. *See* Camilleri 2013, Ex. C. Gastroparesis also can be idiopathic, which means the underlying cause is unknown.

Certain medications—including GLP-1RAs—can affect gastric emptying and may be associated with symptoms that mimic those of gastroparesis. *See* Schol 2025, Ex. E. Drug effects on gastric motility resolve after treatment cessation and are not associated with permanent injury or damage to stomach muscles or nerves. Siegel Dep., Ex. F, at 79:2-8; Raines Dep., Ex. G, at 110:15-24, 145:14-25, 265:1-7; Nguyen Rpt., Ex. H, at 16.

II. GASTROINTESTINAL SYMPTOMS ARE NON-SPECIFIC AND CANNOT BE USED TO DIAGNOSE GASTROPARESIS.

The most commonly reported symptoms associated with gastroparesis, regardless of

[2] A person has delayed gastric emptying when, four hours after eating, more than 10% of a meal remains in her stomach. *Gastric Emptying Study*, Cleveland Clinic, https://my.clevelandclinic.org/health/diagnostics/gastric-emptying-study (last visited Mar. 4, 2025).

etiology, are satiety, nausea, vomiting, bloating and upper abdominal discomfort. *See* Camilleri 2022, Ex. B. As Plaintiffs' experts concede, these symptoms are non-specific and overlap closely with those of many other gastrointestinal conditions, including gastric ulcers, gastric cancer, gallstones, pancreatitis, epigastric pain syndrome, post-prandial distress syndrome, chronic nausea and vomiting syndrome, cyclic vomiting syndrome, cannabinoid hyperemesis syndrome, rumination syndrome, anorexia, and bulimia. *See* Raines Dep., Ex. G, at 98:22-99:2; Siegel Dep., Ex. F, at 49:1-10; *see also* Cangemi 2023, Ex. I; Parkman 2004, Ex. J; Schol 2025, Ex. E. For this reason, as Dr. Siegel acknowledged, symptoms alone cannot be used to predict whether a patient has delayed gastric emptying, or to diagnose gastroparesis. *See* Siegel Dep., Ex. F, at 257:4-11, 173:1-13.

Gastrointestinal symptoms are known side effects of many medications, including GLP-1RAs. A number of different mechanisms have been associated with these symptoms, including direct effects in the brain ("centrally-mediated"), irritation of the stomach lining, and effects on gastric motility. To this point, a recent study conducted by leading researchers at the Mayo Clinic found that only 35% of patients who experienced gastroparesis-like symptoms while taking GLP-1RAs had delayed gastric emptying. Ex. A, Lupianez-Merly 2024. For the other 65%, the symptoms were caused by another mechanism. Although Plaintiffs' experts claim the study (which was published in abstract form) had limitations, they were unable to identify any contrary data or other evidence suggesting that symptoms are reliably predictive of delayed gastric emptying in patients taking GLP-1RAs. *See* Siegel Dep., Ex. F, at 153:25-154:1; Raines Dep., Ex. G, at 251:9-16.

Given the non-specific symptoms and multiple alternative causes, gastroparesis frequently is misdiagnosed in real-world clinical practice. *See* Siegel Dep., Ex. F, at 165:18-24; Raines Dep.,

Ex. G, at 282:14-19. A 2023 study conducted by leading gastroenterologists at the Mayo Clinic found that, among patients referred for the evaluation of gastroparesis, only 20% had the condition. Cangemi 2023, Ex. I. The remaining 80% ultimately were diagnosed with other conditions, including functional dyspepsia (44.5%), rapid gastric emptying (12.1%), and pelvic floor dysfunction (9.9%). *Id.* In 5.1% of the patients, the symptoms were attributed to a medication effect. *Id.* Critically, the authors concluded that "there was no difference in gastrointestinal symptoms on presentation between the patient groups" and that their "findings reaffirm guidelines noting that [gastroparesis] cannot be diagnosed based on symptoms alone." *Id.*

III. GASTROPARESIS DIAGNOSIS REQUIRES A GASTRIC EMPTYING STUDY.

During the past two decades, leading gastroenterology societies have issued guidelines for the diagnosis of gastroparesis. These guidelines consistently have concluded that a gastric emptying study is required to make a diagnosis of gastroparesis.

In 2004, the American Gastroenterological Association (AGA) issued guidelines noting that gastroparesis is a "symptomatic chronic disorder of the stomach characterized by delayed gastric emptying in the absence of mechanical obstruction." Parkman 2004, Ex. J, at 1592. The guidelines explained that gastroparesis symptoms are nonspecific and outlined a diagnostic approach to gastroparesis premised on "demonstrating delayed gastric emptying" and "exclusion of other potential etiologies of symptoms." *Id.* at 1592-1594. In 2013, the American College of Gastroenterology (ACG) issued its own guideline, which explained that "[d]ocumented delay in gastric emptying is required for the diagnosis of gastroparesis." Camilleri 2013, Ex. C, at 21.

In 2021, the United European Gastroenterology and European Society of Neurogastroenterology and Motility issued guidelines for the diagnosis and treatment of gastroparesis. Those guidelines again concluded that an "abnormal [gastric emptying] test is mandatory for establishing a diagnosis of gastroparesis." Schol 2021, Ex. K, at 293. Experts

from North America responded, agreeing that "exclusion of gastric or small intestinal obstruction, upper gastrointestinal endoscopy, and gastric emptying testing (by scintigraphy or breath test, but not by wireless motility capsule or ultrasound) [are] mandatory for establishing a diagnosis of gastroparesis[.]" Camilleri 2021, Ex. L, at 4.

In 2022, the ACG issued new guidelines intended to "document, summarize, and update the evidence and develop recommendations for the clinical management of [gastroparesis], updating the 2013 ACG guideline on [gastroparesis]." Camilleri 2022, Ex. B, at 1198. Those guidelines again concluded that objective evidence of delayed gastric emptying obtained by way of a gastric emptying study is required to diagnose gastroparesis. *Id*.

Around the same time, the AGA issued a clinical practice update on the management of medically refractory gastroparesis. Consistent with the ACG guidelines, the AGA recommended that clinicians evaluating patients with refractory gastroparesis "review symptoms and evaluate physical examination findings to exclude disorders that can mimic medically refractory gastroparesis" and "verify appropriate methodology of the gastric emptying study to ensure an accurate diagnosis of delayed gastric emptying." Lacy 2022, Ex. M, at 491.

Also around the same time, the Rome Foundation[3] initiated the process of developing consensus guidelines on idiopathic gastroparesis (i.e., gastroparesis of unknown cause) and invited the major international neurogastroenterology and motility societies to participate.[4] Ultimately,

[3] Founded in 1996, the Rome Foundation is a leading international organization dedicated to creating scientific data and educational information to assist in the diagnosis and treatment of functional disorders of the gut. *About the Rome Foundation*, https://theromefoundation.org/about/ (last visited Mar. 4, 2025).

[4] These included the Australasian Neurogastroenterology and Motility Association, the Asian Neurogastroenterology and Motility Association, the American Neurogastroenterology and Motility Society, the European Society for Neurogastroenterology and Motility, and Sociedad Latinoamericana de Neurogastroenterología. Schol 2025, Ex. E.

the Consensus group affirmed that "[b]y definition, gastroparesis implies an objective delay in gastric emptying in the absence of mechanical obstruction, and requires both an assessment of gastric emptying and confirmation of the absence of gastric outlet obstruction or another mechanical factor, most commonly through an upper endoscopy." Schol 2025, Ex. E, at 70. The Consensus group further noted that "symptoms of gastroparesis lack specificity" and that "a demonstration of delayed gastric emptying is necessary for diagnosis." *Id*.

As Plaintiffs' experts acknowledge, none of the guidelines suggest that a diagnosis of gastroparesis (regardless of cause) can be made without performing a gastric emptying study. *See* Raines Dep., Ex. G, at 171:2-172:2; Siegel Dep., Ex. F, at 173:1-13. Nor do the guidelines suggest, as Plaintiffs' experts claim, that a diagnosis of drug-induced gastroparesis (or delayed gastric emptying) can be made based on symptoms alone. *See* Raines Dep., Ex. G, at 171:2-172:2, 176:13-177:8. Indeed, as part of its review of a potential safety signal related to aspiration with GLP-1RAs (which involved assessment of the medicines' effects on gastric emptying), in December 2023, FDA's Office of Pharmacovigilance and Epidemiology observed that:

- "Gastroparesis (GP) is characterized by symptoms (e.g., post-prandial fullness, nausea, vomiting, and upper abdominal pain) and objective documentation of delayed gastric emptying of solid food without mechanical obstruction";
- "For symptomatic patients without evidence of mechanical obstruction, the gold standard for evaluation of delayed gastric emptying is scintigraphy, although alternative methods of evaluation (i.e., wireless motility capsule, stable isotope breath test,

functional ultrasonography) can be performed"; and,

- "the presence of retained food is considered supportive but not diagnostic for GP."

Ex. N, at 2.[5]

IV. PLAINTIFFS' EXPERTS AND THEIR OPINIONS.

For purposes of this issue, Plaintiffs submitted reports from three experts: (1) Dr. Ronnie Fass, a gastroenterologist in Ohio; (2) Dr. Daniel Raines, a gastroenterologist in Louisiana; and (3) Dr. Eliot Siegel, a radiologist in Maryland. Dr. Fass was subsequently withdrawn as an expert, leaving Dr. Raines and Dr. Siegel to sit for depositions. Although both acknowledge that diagnosis of gastroparesis requires evidence of delayed gastric emptying, both contend that a diagnosis of drug-induced gastroparesis can reliably be made without performing a gastric emptying study. Raines Rpt., Ex. D, at 14; Siegel Rpt., Ex. O, at 25.

A. Plaintiffs' Experts' Backgrounds and Qualifications.

Dr. Raines is an Assistant Professor in the Louisiana State University Department of Medicine, Section of Gastroenterology. Raines Rpt., Ex. D, at 1. He attended medical school at LSU Shreveport School of Medicine and completed his residency and fellowship at University of Alabama at Birmingham (Internal Medicine) and LSUHSC (Gastroenterology), respectively. He is board certified in Internal Medicine and Gastroenterology.

Dr. Siegel is the Chief of Radiology and Nuclear Medicine, Veterans Affairs, Maryland Healthcare System, and a Professor and Vice Chair at the University of Maryland School of

[5] The FDA Pharmacovigilance, Epidemiology, and Drug Utilization Review titled "Regurgitation and pulmonary aspiration of gastric contents during general anesthesia and deep sedation" was completed on December 14, 2023. The document was received by Novo Nordisk on February 27, 2025, in response to a FOIA request submitted on September 9, 2024. The full set of documents received from FDA in response to that request is attached to the Declaration of Lucas P. Przymusinski, M.D., J.D. as Ex. N.

Medicine, Department of Diagnostic Radiology. Siegel Rpt., Ex. O, at 3. He completed medical school, his residency, and his fellowship at the University of Maryland. His relevant experience is that he has interpreted more than 1,000 gastric emptying studies. Siegel Dep., Ex. F, at 39:23-41:6. He has no formal training in gastroenterology or internal medicine and has not published any articles on gastroparesis. *Id*. at 67:8-20, 211:23-212:12, 21:4-10.

B. Plaintiffs' Experts' Diagnostic Methodologies for "Drug-Induced Gastroparesis."

Although they acknowledge that evidence of delayed gastric emptying is required to make a diagnosis of gastroparesis, each expert contends that a diagnosis of "drug-induced gastroparesis" reliably can be made without need for a gastric emptying study. In other words, they contend that they can impute the presence of delayed gastric emptying based on symptoms and medication use alone, obviating the need for an objective gastric emptying study.

According to Dr. Raines, "drug-induced gastroparesis" is a temporary condition that typically resolves within a matter of weeks after treatment cessation.

> Q. So with what you called a drug-induced gastroparesis, is that a temporary entity, a medical condition?
>
> A. In my experience, when you withdraw the drug, most patients get better or their symptoms completely resolve.
>
> Q. In your experience, if you're diagnosing based on your standard of care, you see drug-induced gastroparesis involving most patients getting better or their symptoms completely resolve upon withdraw of the drug, true?
>
> A. Yes.

Raines Dep., Ex. G, at 110:15-24; *see also id.* at 145:14-25, 146:8-12. The temporary nature of the drug effect distinguishes what Dr. Raines describes as "drug-induced gastroparesis" from other forms of gastroparesis and, in his opinion, lends itself to a different diagnostic approach:

> In patients who experience symptoms of gastroparesis which correlate with GLP-1RA therapy, my first step is to withdraw the drug. Improvement in symptoms following withdrawal of an offending drug supports a diagnosis of drug-induced gastroparesis and obviates the need for additional testing. In patients with other

> forms of gastroparesis, I routinely order an upper endoscopy and/or imaging to evaluate for organic pathology and mechanical obstruction. I utilize GES studies to document delay in gastric emptying and assess severity of delay.

Raines Rpt., Ex. D, at 14; *see also* Raines Dep., Ex. G, at 141:12-18.

If gastrointestinal symptoms start shortly after the initiation of GLP-1RA therapy and then abate after treatment cessation, Dr. Raines attributes those symptoms to the medication's effect on gastric emptying (without any further testing) and makes a diagnosis of "drug-induced gastroparesis":

> Q. So if I understand that correctly, Dr. Raines, because you're aware that GLP-1 medication is [sic] delayed gastric emptying, you then conclude that a patient who experiences nausea and vomiting at or around the time when they start the medication or increase their dose, their symptoms must be a result of delayed gastric emptying; is that correct?
>
> MS. AMINOLROAYA: Object to form.
>
> THE WITNESS: I think using "must" makes it sounds like it's so absolute. So it's like it makes sense or that—it's more likely than not that that's why they have those symptoms.

Raines Dep., Ex. G, at 252:3-14. Ultimately, however, Dr. Raines concedes the only mandatory criteria for diagnosis is a temporal relationship between symptoms and medication use.

> Q. The more severe the GI-related symptoms, the more likely you are to conclude that they're suffering from drug-induced gastroparesis?
>
> A. The more classic their presentation is for drug-induced gastroparesis, the more likely.
>
> Q. It seems circular to me, sir.
>
> A. I know, me, too. So it's like—there's a certain threshold, like, yes. They have to have symptom onset with the drug.

Id. at 142:3-11.

Dr. Siegel takes this a step further. In his view, if a patient presents with gastrointestinal symptoms while taking a GLP-1RA medication, then the presumptive diagnosis is drug-induced gastroparesis. *See* Siegel Dep., Ex. F, at 75:7-11. Although resolution of symptoms is expected, it is not necessary. *See id.* at 80:2-16, 82:14-19, 83:3-9. This is true despite the fact that he admits

that there may be different mechanisms beyond delayed gastric emptying by which medications such as GLP-1RAs cause gastrointestinal symptoms. *See id.* at 248:21-251:22. And although he pays lip service to temporality and ruling out alternative causes, he admits neither is required for him to make a diagnosis of "drug-induced gastroparesis." *See id.* at 156:14-157:16; 275:9-21. In his clinical practice, however, Dr. Siegel never has diagnosed a patient with gastroparesis without performing a gastric emptying study, nor for that matter has he ever diagnosed a patient with "drug-induced gastroparesis." *Id.* at 191:4-12.

LEGAL STANDARD

The proponent of expert evidence bears the burden of demonstrating, first, that the "expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;" second, that the proposed testimony is "based on sufficient facts or data;" third, that it is "the product of reliable principles and methods;" and, finally, that the expert has "reliabl[y] appli[ed]" "principles and methods to the facts of the case." Fed. R. Evid. 702. Because expert testimony has the potential to "be both powerful and quite misleading," the Court must perform the critical role of "gatekeeper," and exclude expert testimony that is not based upon reliable methodology and closely tied to the issues in the case. *Daubert*, 509 U.S. at 595-98; *Oddi v. Ford Motor Co.*, 234 F.3d 136, 144 (3d Cir. 2000). Although publication is not dispositive of reliability, "submission to the scrutiny of the scientific community is a component of 'good science,' in part because it increases the likelihood that substantive flaws in methodology will be detected." *Daubert*, 509 U.S. at 593.

The Third Circuit has described eight non-exhaustive factors that the Court assesses to determine whether an expert's testimony is sufficiently reliable: "(1) whether a method consists of a testable hypothesis; (2) whether the method has been subject to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's

operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put." *In re Paoli*, 35 F.3d at 742 n.8.

An MDL court has particular latitude to require specific diagnostic criteria given the needs of managing a large docket. For example, the district court in *In re Asbestos* relied on "generally accepted medical standards" as well as "statements from reputable medical organizations" when interpreting its order to require a detailed exposure history and to determine that "pleural plaques" or "thickening" did not meet the definition of an asbestos-related disease. *In re Asbestos Prods. Liab. Litig. (No. VI)*, 718 F.3d 236, 242, 245 (3d Cir. 2013). The Third Circuit affirmed the district court's dismissal of plaintiffs' claims for failing to produce evidence that satisfied the prevailing scientific consensus for identifying an asbestos-related injury. *Id.* at 245-46; *see also In re Nat'l Football League Players Concussion Injury Litig.*, No. 23-1585, 2025 WL 560631, at *1 (3d Cir. Feb. 20, 2025) (non-precedential) (affirming where district court found settlement agreement required specific post-mortem diagnostic test). Similarly, in a case where the plaintiffs alleged silica-related injuries, plaintiffs' experts relied on positive radiographic findings as one of the factors in their standard of diagnosis for the alleged injury. *In re Silica Prods. Liab. Litig.*, 398 F. Supp. 2d 563, 589-90 (S.D. Tex. 2005). However, as the court noted, radiological findings consistent with silicosis may be caused by other conditions aside from silica exposure. *Id.* at 631. Thus, the standard of diagnosis for silicosis required more to rule out other causes. *Id.* at 623, 631.

ARGUMENT

Plaintiffs' own experts concede that objective testing that shows delayed gastric emptying is needed to diagnose chronic gastroparesis, the injury that appears to be at issue in the vast majority of cases filed to date in this MDL. Indeed, Plaintiffs have not come forward with any

expert who contends that a diagnosis of chronic gastroparesis can be made without a gastric emptying study. Accordingly, this should resolve Issue 1 for those Plaintiffs in this MDL who allege chronic gastroparesis as their injury.

But even as to the condition they describe as temporary "drug-induced gastroparesis," Plaintiffs' experts' diagnostic "methodologies" fall far short of the reliability requirements set forth in Rule 702, as well as in *Daubert* and its progeny. First, Plaintiffs' experts' methodologies lack critical hallmarks of reliability, including lack of testing, lack of error rate, and lack of peer review, and they are at odds with clinical guidelines issued by leading medical associations in the United States and internationally. Second, the methodologies are subjective and standardless, reflecting an outcome-driven approach that is unacceptable under Rule 702. Third, the experts have no evidentiary basis for their claim that they can diagnose gastroparesis based on a temporal relationship between GLP-1RA medicine use and the onset of non-specific gastrointestinal symptoms; moreover, the experts describe this purported temporal relationship in a manner so vague, inconsistent, and standardless that it hardly qualifies as a methodology, much less one that could meet Rule 702's standards for reliability. Finally, Dr. Siegel's opinions should be excluded for additional reasons due to his lack of relevant qualifications and lack of rigor.

V. PLAINTIFFS' EXPERTS' DIAGNOSTIC "METHODOLOGIES" LACK CRITICAL INDICIA OF RELIABILITY UNDER RULE 702 AND *DAUBERT*.

Plaintiffs' experts' diagnostic "methodologies" lack critical indicia of reliability under *Daubert* and its progeny, including absence of testing, lack of known error rate, and lack of peer review, and, moreover, they run contrary to the consensus diagnostic guidelines adopted by the leading national and international medical societies. *See* 509 U.S. at 593-94.

In this case, Plaintiffs' experts concede that none of the diagnostic guidelines issued over the past twenty years by leading experts in the field of gastrointestinal motility describe their

symptom-based methodology for diagnosing gastroparesis. Raines Dep., Ex. G, at 171:2-172:2, 176:13-177:8; Siegel Dep., Ex. F, at 102:17-25, 113:6-18. On the contrary, all guidelines recognize that a gastric emptying study is required to make a diagnosis of gastroparesis. *See supra* at pp. 5-8. Plaintiffs' experts dismiss these guidelines as inapplicable to this MDL and specifically to the diagnosis of drug-induced gastroparesis. *See, e.g.*, Raines Dep., Ex. G, at 131:10-23, 152:5-12; Siegel Dep., Ex. F, at 113:6-18. But neither expert could point to a single publication supporting his view or outlining his symptom-based diagnosis methodologies. Notably, Dr. Raines acknowledged that he never has previously offered an opinion that deviated from a consensus guideline. Raines Dep., Ex. G, at 53:23-54:2.

With that context in mind, it is important to note that Plaintiffs' experts' diagnostic methodologies never have been published or submitted for peer review in any form. Siegel Dep., Ex. F, at 277:16-23; Raines Dep., Ex. G, at 162:21-25, 126:18-127:1; *Daubert*, 509 U.S. at 593. Moreover, neither Dr. Raines nor Dr. Siegel tested their methodologies to determine how accurate they are in differentiating drug-induced gastroparesis from the many other conditions that share the same non-specific gastrointestinal symptoms. Siegel Dep., Ex. F, at 125:10-16; Raines Dep., Ex. G, at 210:2-17, 212:4-22. And neither expert was aware of anyone who has tested the accuracy of their methodology in any form.

> Q. [Y]ou're not aware of any study that has taken your diagnostic methodology predicated on symptoms and history and tested how reliable it is in predicting the extent of delay in gastric emptying, correct?
> A. Correct. I mean, I would, through inference of other data that I've seen and what I've read, you know, believe that that study would be of limited value. But I have not seen that particular study done, nor would I feel as though I would want to conduct it.

Siegel Dep., Ex. F, at 261:5-14.

> Q. In the context of this methodology, which you're putting forward as a standard of care in your report, I want to know, is there any peer-reviewed literature, published literature, that I can go to to determine whether the method is accurate,

> and if so, how often it's right and how often it's wrong?
> MS. AMINOLROAYA: Objection. Asked and answered several times now.
> THE WITNESS: No.

Raines Dep., Ex. G, at 213:22-214:5. This lack of testing stands in stark contrast to the Supreme Court's explanation that "whether [a theory or technique] can be (and has been) tested" is the "methodology [that] distinguishes science from other fields of human inquiry." *Daubert* 509 U.S. at 593.

Not surprisingly, considering the lack of testing, neither expert could provide any estimate of how accurate his method is, what its error rate is in clinical application, or, more to the point, how often they would be wrong if they applied it in this litigation. Siegel Dep., Ex. F, at 261:15-262:7; Raines Dep., Ex. G, at 210:18-211:4, 212:4-22. This fact alone "counsels strongly against admissibility of [their] opinions." *Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 570 (W.D. Pa. 2003).

Moreover, both experts acknowledge that a recent study conducted by researchers at the Mayo Clinic found that the presence of symptoms (such as nausea, vomiting, and abdominal pain) in patients taking GLP-1RA medicines—the very factors Plaintiffs' experts claim to rely on for making a diagnosis of drug-induced gastroparesis—was an extremely poor predictor of delayed gastric emptying and thus gastroparesis. Ex. A, Lupianez-Merly 2024; *see also* Siegel Dep., Ex. F, at 150:2-9, 150:24-151:22, 153:25-154:1; Raines Dep., Ex. G, at 249:10-23. The error rate of 65% reported in this study indicates that a physician attempting to make a diagnosis based on the presence of gastroparesis-like symptoms, without performing a gastric emptying study, would be wrong two-thirds of the time, a result far worse than flipping a coin. Ex. A, Lupianez-Merly 2024. An error rate of this magnitude is unacceptable under *Daubert*. 509 U.S. at 594; *see also In re Zostavax* (*Zoster Vaccine Live*) *Prods. Liab. Litig.*, 579 F. Supp. 3d 675, 679 (E.D. Pa. 2021)

(citing *Heller v. Shaw Indus., Inc*., 167 F.3d 146, 156 (3d Cir. 1999) (explaining that an expert must reliably rule out alternative causes of the alleged condition).

In sum, Plaintiffs' experts' opinions lack critical indica of reliability under *Daubert* and properly should be viewed with skepticism.[6]

VI. PLAINTIFFS' EXPERTS' DIAGNOSTIC "METHODOLOGIES" LACK ANY OBJECTIVE STANDARDS BEYOND A VAGUE TEMPORAL RELATIONSHIP.

As discussed above, both experts claim they can reliably diagnose drug-induced gastroparesis without conducting a gastric emptying study. The methodologies they put forward to accomplish this are entirely outcome driven and devoid of any "standards controlling the technique's operation" beyond the presence of a vague temporal relationship between symptom onset and medication use. *In re Paoli*, 35 F.3d at 742 n.8.

A. Dr. Raines's Diagnostic Methodology Is Entirely Subjective, with the Exception of a Vague Requirement for Temporality.

During his deposition, Dr. Raines repeatedly answered questions about his diagnostic methodology with some variation of the phrase "it depends"—be it on the case, on the context, or on something else. Raines Dep., Ex. G, at 107:13-20, 109:7-12, 115:21-116:6, 118:6-14, 118:25-119:2, 136:24-137:3, 137:24-138:10. The one exception to this pattern was in the context of what he referred to as a "classic" case: "All I can say is it depends on the case, except for if we describe a classic case, then, yes, I can make that diagnosis, and then if we generalize that to every patient, then that's a different story." *Id.* at 118:6-14.

So, what is this "classic" case where, according to Dr. Raines, a diagnosis of drug-induced

[6] As numerous courts have held, and as Lilly explains in its Brief, calling a methodology "differential diagnosis" is not sufficient to establish reliability. Here, Plaintiffs' experts have not come forward with a reliable method for ruling in gastroparesis (or ruling out other causes of gastroparesis-like symptoms) in the absence of a gastric emptying study. Indeed, as Plaintiffs' experts acknowledged, all clinical guidelines require a gastric emptying study for diagnosis.

gastroparesis can be made without a gastric emptying study? Dr. Raines was asked this very question at his deposition. His answers highlighted several key factors—including vomiting of undigested food, presence of severe gastrointestinal symptoms, and the absence of other risk factors or conditions—that he considers characteristic of such "classic" presentation.

> Q. What's a classic presentation?
>
> A. So a patient that we described previously with no other health symptoms, no risk factors for gastric cancer, gastric ulcer, gallstones, pancreatitis, no history of anything to suggest any other diagnosis, other than drug-induced gastroparesis, starts taking a drug, has severe symptoms of nausea, vomiting, abdominal pain, vomits food eaten four hours prior, has no fever, has no abdominal tenderness, and so that correlation of starting a drug and being severely sick with those kind of typical symptoms, that would be consistent with a diagnosis of drug-induced gastroparesis, and really no features of anything else or no suggestion of any other diagnosis, that's alternative.

Id. at 114:5-17

> Q. You think you can reach a conclusion more likely than not that nausea and vomiting onset in temporal correlation with the use of a GLP-1 RA medication is sufficient to reach a diagnosis of drug-induced gastroparesis?
>
> A. Yes. In the criteria that I described. So chronic nausea and vomiting, onset of the drug. Really no other reason to have this presentation. And particularly vomiting solid food.

Id. at 144:1-9; *see also id.* at 115:7-20. As the deposition went on, however, it became clear that Dr. Raines does not in fact require any of these criteria to be satisfied and, just as importantly, that no "standards [exist] controlling its operation." *Daubert*, 509 U.S. at 580.

To begin with, although he initially said it was "particularly" important, Dr. Raines eventually testified that vomiting of solid food is not necessary to make a symptom-based diagnosis. *See* Raines Dep., Ex. G, at 162:10-13. Dr. Raines also acknowledged that he does not have any system for evaluating the overall severity of a patient's symptoms in the context of making a gastroparesis diagnosis; he would just know gastroparesis when he saw it. *See id.* at 141:12-18. He even conceded that his symptom-based criteria were "circular" and that the only

real "threshold" for making a diagnosis is the presence of a temporal relationship.

> Q. The more severe the GI-related symptoms, the more likely you are to conclude that they're suffering from drug-induced gastroparesis?
> A. The more classic their presentation is for drug-induced gastroparesis, the more likely.
> Q. It seems circular to me, sir.
> A. I know, me, too. So it's like—there's a certain threshold, like, yes. They have to have symptom onset with the drug.

See id. at 142:3-11. And, with respect to the temporal relationship, Dr. Raines was unwilling to provide any boundaries, describing the length of time from drug initiation to symptom onset as just a "factor" that he would consider in his "assumption" about the diagnosis of drug-induced gastroparesis. *See id.* at 207:23-208:9.

Dr. Raines also indicated that the presence of other risk factors or medical conditions would not be dispositive, though they might "influence" his opinion. *See id.* at 235:10-25. When asked how the presence of other risk factors or conditions would "influence" his opinion (*i.e.*, how he would weigh those factors), Dr. Raines responded: "that's a great question." *See id.* at 239:10-19. After a lengthy effort to prompt him to explain further, Dr. Raines eventually admitted that any such evaluation would be subjective; in his view, "that's just how medicine is practiced, yeah." *See id.* at 239:10-241:8, 236:20-237:3.

For this reason alone, Dr. Raines's methodology is unreliable, and his opinions should be excluded. *See Joiner*, 522 U.S. at 146 ("[N]othing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert."); *In re Rezulin Prods. Liab. Litig.*, 369 F. Supp. 2d 398, 437 (S.D.N.Y. 2005) (excluding expert opinion that was subjective and standardless).

B. Dr. Siegel's Diagnostic Methodology Has No Criteria at All.

Dr. Siegel is no better. Indeed, his methodology has no criteria at all, beyond the presence

of gastrointestinal symptoms during GLP-1RA therapy. Siegel Dep., Ex. F, at 75:7-11. For example, Dr. Siegel testified that, with drug-induced gastroparesis, he would expect symptoms to resolve after treatment cessation. *Id.* at 79:2-8. But he later admitted that lack of symptom resolution would not prevent him from making a diagnosis. *Id.* at 80:2-16 ("I don't believe that there's any hard and fast rules about determining whether or not it was due to gastric emptying based on how a patient responds after the medication is withdrawn."); *see also id.* at 82:14-19, 83:3-9. Eventually, Dr. Siegel testified that he does not even need evidence of classic gastroparesis symptoms or a temporal relationship to make a diagnosis of drug-induced gastroparesis:

> Q. So you would look at more information than just this. But what you—the minimum that you require in order to diagnose gastroparesis without any kind of gastric emptying study in GLP-1 receptor agonist patients is a certain constellation of classic gastroparesis symptoms and a certain temporal relationship, true?
>
> MR. BUXNER: Object to form. Misstates. Asked and answered. Go ahead, Doctor.
>
> THE WITNESS: So those would be really important components.
>
> * * *
>
> BY MS. FITZPATRICK: Q. You can look—there might be other things that exclude somebody, but you need those, right?
>
> MR. BUXNER: Object to form.
>
> THE WITNESS: I don't believe that's the case. I think one could have a temporal relationship or one could—in other words, I don't think you need all of that. I think in each individual patient—and we could—you know, we'd have to discuss the specific case study. Then I could tell you whether or not I would diagnose gastroparesis in that patient without a gastric emptying study in a patient where I thought that I should withdraw the medications and there not be a need for gastric emptying studies.

Id. at 156:14-157:16. Tellingly, Dr. Siegel would not even provide a cutoff for what he would consider to be a temporal relationship supporting a diagnosis of drug-induced gastroparesis—"I think you're trying to pin down a specific time limit and I really don't have one." *Id.* at 275:9-21, 274:5-22. In his opinion, apparently, symptoms developing even years after medication initiation could be considered temporally related to the medicine. *Id.* at 275:9-276:11.

Thus, as with Dr. Raines, Dr. Siegel's methodology is entirely standardless, and, for that reason, his opinion that drug-induced gastroparesis can be diagnosed without a gastric emptying study should be excluded. *See Lipitor (Atorvastatin Calcium) Mktg. v. Pfizer, Inc.*, 892 F.3d 624, 634 (4th Cir. 2018) ("Result-driven analysis, or cherry-picking, undermines principles of the scientific method and is a quintessential example of applying methodologies (valid or otherwise) in an unreliable fashion."); *In re Acetaminophen – ASD-ADHD Prods. Liab. Litig.*, 707 F. Supp. 3d 309, 336 (S.D.N.Y. 2023); *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, No. 12-MD-2342, 2015 WL 7776911, at *16 (E.D. Pa. Dec. 2, 2015) (explaining that "[i]t is improper for an expert to take a results-driven approach to a question, molding his methodology and selectively relying upon data so as to confirm his preconceived opinion").

C. Plaintiffs' Experts' Reliance on a Vague Temporal Relationship Is Insufficient.

While a temporal relationship may theoretically be sufficient to associate medication use with the onset of certain gastrointestinal symptoms, that is not equivalent to a diagnosis of gastroparesis. To diagnose gastroparesis, a physician has to have a reliable basis to conclude that the symptoms are attributable to a delay in gastric emptying, as opposed to some other cause. As Dr. Raines explained, "Delayed gastric emptying is a defining feature of all subtypes of gastroparesis" and evidence of delayed gastric emptying is required to make a diagnosis of gastroparesis. Raines Rpt., Ex. D, at 11; *see also* Raines Dep., Ex. G, at 100:10-13.

Plaintiffs' experts bypass this critical requirement, describing gastrointestinal symptoms that occur in some vague temporal proximity to medication use as "drug-induced gastroparesis":

> Q. So there's a difference, Doctor, between saying symptoms are related to the drug and saying the symptoms are related to the drug and your diagnosis is drug-induced gastroparesis. You see the difference, right?
> MS. AMINOLROAYA: Objection.
> THE WITNESS: I see the difference, and I would use the term "drug-induced

> gastroparesis," and it's obviously that you have a different opinion that you wouldn't use that term.

Id. at 209:12-21. That opinion requires an unsupported leap in logic that assumes gastrointestinal symptoms occurring during GLP-1RA treatment are necessarily a result of the medication's effect on gastric emptying. But, as both Dr. Raines and Dr. Siegel acknowledged, medications can cause gastrointestinal symptoms in a variety of ways that do not involve delayed gastric emptying, including specifically through a direct effect on nausea centers in the brain. Raines Dep., Ex. G, at 99:24-100:4, 106:22-107:8; Siegel Dep., Ex. F, at 248:21-251:22.

Tellingly, neither Dr. Raines nor Dr. Siegel came forward with any evidence to support their assumption that gastrointestinal symptoms reliably can predict delayed gastric emptying in patients taking GLP-1RA medicines. On the contrary, as discussed above, the Lupianez-Merly study found that approximately two-thirds of patients who experienced gastrointestinal symptoms on a GLP-1RA ***did not*** have delayed gastric emptying and, thus, by definition, ***did not*** have gastroparesis. Ex. A, Lupianez-Merly 2024; *see also supra* at pp. 2, 4. Although they argued that the study had limitations, Plaintiffs' experts could not identify any data they considered more reliable. As Dr. Raines explained, "I don't know if there's a lot of literature pertaining to that specific data point." Raines Dep., Ex. G, at 251:9-16.

Likewise, although he claimed that vomiting undigested food four hours after a meal is pathognomonic of delayed gastric emptying, Dr. Raines acknowledged that he could not identify any support for that claim. Raines Dep., Ex. G, at 101:23-102:10.

> Q. Well, Doctor, I understand that you believe it's a factor, and I understand what you're saying here. What I'm asking is: Can you point to any data, any publications, any article, any peer-reviewed materials, that say that vomiting of undigested food four hours after a meal is pathognomonic for delay in gastric emptying?
>
> MS. AMINOLROAYA: Objection. Asked and answered.
>
> THE WITNESS: I don't see that statement. Like I can't quote a statement from

> like—exactly like that from a particular article.
>
> * * *
>
> Q. Sure. But you still haven't answered my question. Are you aware of a study that's actually tested how reliable a predictor this symptom is of the presence of delayed gastric emptying?
>
> A. I'm not aware of a study that shows that. So many people vomited undigested food four hours after eating and then they have gastric emptying studies to kind of correlate the two findings.
>
> Q. So the answer's no?
>
> A. Correct.

Id. at 217:9-19, 220:25-221:9.

In sum, an irreconcilable analytical and evidentiary gap exists between Plaintiffs' experts' symptom-based opinions and the evidence required to establish a reliable diagnosis of drug-induced gastroparesis. *See Joiner*, 522 U.S. at 146 ("A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered.").

VII. DR. SIEGEL'S OPINIONS—WHETHER RELATED TO CHRONIC OR "DRUG-INDUCED" GASTROPARESIS—SHOULD BE EXCLUDED FOR ADDITIONAL REASONS.

In addition to the reasons discussed above, Dr. Siegel's opinions should also be excluded as he is not qualified to offer opinions on the diagnosis of gastroparesis; his opinions are inconsistent with his clinical work outside of the courtroom; he applied a lower level of rigor to preparing his expert report than to his outside publications; and he did not sufficiently review the very literature he cited in support of his opinions.

An expert's qualifications may impact the reliability of his methodology. *In re Paoli*, 35 F.3d at 742 n.8. Dr. Siegel is a radiologist who has no formal training in gastroenterology (let alone in motility disorders) or even internal medicine. Siegel Dep., Ex. F, at 67:18-20, 211:23-212:12. As he readily acknowledges, he has not authored any guidelines for the diagnosis of gastroparesis or even been asked to participate in drafting such guidelines. *Id.* at 277:2-15. And, contrary to his claims here, Dr. Siegel admits that he has never diagnosed a patient with

gastroparesis without conducting a gastric emptying study or, for that matter, ever made a diagnosis of "drug-induced gastroparesis." *Id.* at 189:18-190:8, 191:4-12, 192:1-6, 199:11-16. Tellingly, he admits that he has never used his symptom-based diagnostic methodology outside the courtroom.

> Q. Ultimately, Doctor, the methodology that you describe for diagnosing drug-induced gastroparesis, whatever your opinion is about the reliability of it, it's not a methodology you've ever actually done to formally diagnose a patient, correct?
>
> MR. BUXNER: Object to form.
>
> THE WITNESS: Yeah. I guess—I think what you're saying is similar to the questions you've been asking; and that is, I work in the context of my role as a radiologist and nuclear medicine physician. And so, the patients that I see in that particular role until now that I've changed to become an oncologist, in that particular role are exclusively patients who have been referred for either one type of imaging study or the other or a consultation related to those imaging studies.

Id. at 202:2-17.

Dr. Siegel also admits that he wrote his report "differently" from how he would prepare a scientific paper or publication because it was "a completely different use case." *Id.* at 97:4-8, 86:1-6, 88:3-7, 96:21-25. Dr. Siegel even acknowledges he did not thoroughly review the studies he cited in support of his opinions, and in some cases reviewed only the "abstract" of the study:

> Q. Okay. And you told me a few minutes ago that the studies that you reviewed and considered relevant, you read and reviewed completely, correct?
>
> A. No. Actually, the ones that I considered I read the parts of those studies that I thought were most relevant to the assignment in the report in detail. But there is no doubt in my mind that there are portions of what I read that I did not believe necessarily related to my report and that I didn't read.
>
> Q. Okay. But certainly, these three studies, that information in them that was relevant to supporting your opinion that drug-induced gastroparesis in patients taking GLP-1 could be diagnosed by symptoms alone, you would have read that because that clearly would have been relevant to your opinion, correct?
>
> A. No.
>
> MR. BUXNER: Object to form. . . .
>
> THE WITNESS: In other words, I don't know what I didn't read. And so, I would have had to have read it in order to have confirmed what you just said. There were sections that were labeled. Sometimes I might have read an abstract. In some cases,

> it's possible that there was an abstract that I didn't have the full text to and just relied on the abstract. So I don't think that I would be accurate if I made that more broad statement.

Id. at 297:3-298:5; *see also id.* at 298:7-20, 306:13-20.

For these reasons also, Dr. Siegel's opinions should be excluded. *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999) (characterizing the gatekeeper objective as making certain "that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field"); *In re Paoli*, 35 F.3d at 742 n.8; *In re Zostavax*, 579 F. Supp. 3d at 680 (finding that expert could "not rely on his experience" when he had "never seen or diagnosed a patient with Zostavax-caused shingles").

CONCLUSION

For all of these reasons, Novo Nordisk respectfully requests that the Court exclude the opinions and testimony of Daniel Raines, M.D. and Eliot Siegel, M.D.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on March 5, 2025, a true and correct copy of the foregoing Memorandum of Law in Support of Novo Nordisk's Motion to Exclude the Opinions and Testimony of Drs. Daniel Raines and Eliot Siegel was electronically filed using the Court's CM/ECF System, which will send notification of such filing to all counsel of record.

/s/ Loren H. Brown
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